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Indications and Limits of Ultrasound-Guided Cytology in the Management of Nonpalpable Thyroid Nodules

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ABSTRACT

Although ultrasound (US)-guided fine needle aspiration biopsy (FNAB) is widely prescribed in nonpalpable thyroid nodules, the goal of this study was to define precisely the indications and limits of US-FNAB in a series of 450 nonpalpable nodules. Among 94 surgically controlled cases, 20 (8 infracentimetric and 12 centimetric or supracentimetric) carcinomas were diagnosed. The diagnosis of malignancy was successfully made by US-FNAB in 16 of 20 carcinomas, 3 were missed because of insufficient cytological material, and 1 was misdiagnosed. US-FNAB sensitivity and specificity were 94% and 63%, respectively. A logistic model indicated that nodule size ($P < 0.6$) was not associated with histological diagnosis, but that solid hypoechoic features were more likely to be malignant ($P < 0.0003$), with US sensitivity and specificity for malignancy of 80% and 70%, respectively. Logistic regression indicated that adequate cytological material significantly increased with nodule size ($P < 0.0001$). This result outlined the limits of US-FNAB in small nodules. Hence, indication of US-FNAB appears judicious in centimetric or supracentimetric nodules or in solid and hypoechoic ones. Such a management would allow the discovery of 15 of 20 carcinomas and would avoid 16% of unnecessary biopsies. (*J Clin Endocrinol Metab* **84:** 24–28, 1999)

FINE needle aspiration biopsy (FNAB) is considered the most reliable test for the diagnosis of malignant thyroid nodule (1–3). In nonpalpable thyroid nodules, ultrasonography has become a main tool for FNAB guidance. Moreover, ultrasonography is the most effective method to provide information about location, number, size, echo structure, and echogenecity of thyroid nodules. As a consequence of the increasing application of ultrasound (US), the prevalence of incidental nodules in the general population has increased (4, 5). Contradictory attitudes have been proposed for the management of nonpalpable thyroid nodules. Some clinicians recommend US-guided FNAB (US-FNAB) in nonpalpable thyroid nodules (6–8), whereas others consider that a simple follow-up neck palpation is sufficient when there is no history of familial thyroid cancer or history of head/neck irradiation (5). The aim of our study was to evaluate the indications and limits of US-FNAB in the management of nonpalpable thyroid nodules in a series of 450 nodules.

Subjects and Methods

Patients

From December 1989 to November 1995, 1741 consecutive patients with thyroid nodules were referred for FNAB in our department. Among them, 450 (26%) patients presented with nonpalpable nodules and underwent US-FNAB. These nodules had been diagnosed by US performed for various reasons (Table 1). Preliminary clinical examination was performed by 2 experienced endocrinologists (L.L. and T.D.) before FNAB to confirm that the nodules were not palpable (387 cases; 86%) or too deeply located (63 cases; 14%) to be reliably biopsied under palpation-guided FNAB. The series included 372 females and 78 males, with a mean age of 49.5 yr (ranging from 16–83 yr).

Methods

US of the thyroid gland was performed using a real-time ultrasonographic scanner (Advanced Technology Laboratory, Washington DC) with a 7.5-MHz linear transducer. All scans were performed in our department by an experienced echographist (T.D.). Among the 450 nodules included in the series, 136 (30%) were solitary, whereas 314 (70%) were associated with other nodules. The echo structure (solid, mixed, or cystic), echogenecity (hyperechoic, isoechoic, or hypoechoic), calcification (presence or absence), and margin (well defined or blurred) were assessed. Cystic nodules were defined as anechoic nodules. The nodule mean diameter was considered the arithmetic mean of the measured length, width, and depth. Volume was estimated through the relation: V = (length × width × depth)/2. After a logarithmic transformation, the nodule volume distribution was Gaussian (mean = −0.058; SD = 0.46). According to the nodule volume, the series was partitioned into 10 quantiles for statistical analysis.

US-FNAB were all performed by the same physician (L.L.), using a 25-gauge needle with a free hand technique. For a partially cystic nodule, the biopsy sampling was directed to the solid portion of the nodule. In patients with more than one nodule, FNAB on only the largest one was retained. During the course of the study, some patients were subjected to repetitive FNAB. In such cases, only the result of the last FNAB was considered.

Material was smeared on slides and stained by May-Grunwald-Giemsa stain. The cytological analysis was always performed by the same pathologist (B.F.). Insufficient cytological material (ICM) was defined as the presence of less than six follicular thyroid cell clusters on the slides. Conversely, cytological material was defined as adequate when six or more thyroid cell clusters were obtained. Adequate cytological material

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TABLE 1. Indications of ultrasonography in the total series

Indications of ultrasonography	No. (%)	Carcinomas (no.)
Total	450 (100)	20
Incidental detection with various imaging techniques in the course of evaluation of an other condition	83 (18)	
Carotid duplex exams, cervical scans	51	4
High risk patients after radiation exposure	13	
Check-up of distant metastasis	10	1
Check-up of cervical adenopathy	9	
Associated palpable nodule	62 (14)	3
Homogenous or multinodular goiter	126 (28)	5
Hyper- or hypothyroidism	36 (8)	2
Follow-up after partial thyroidectomy	40 (9)	2
Questionable indications (mild obesity, no medical reasons, anxiety, symptoms from otorhinolaryngologist sphera)	76 (17)	3
Doubtful palpation of the thyroid gland that was proved to be normal by two trained endocrinologists	27 (6)	

(ACM) was classified as benign, malignant, or suspicious. Benign cytological results corresponded to colloid or macrofollicular adenomas, nodular and/or cystic goiters, or thyroiditis. Malignant cytological results corresponded to diagnosis of papillary carcinoma, high grade follicular carcinoma, or medullary or anaplastic carcinoma. Suspicious cytological results corresponded to smears with a high cellularity, microacinar formation, a scanty or absent colloid, large nuclei and noticeable anisocaryosis, and/or a dominance of Hurthle cells. Suspicious cytological results were handled as malignant diagnoses for statistical analysis.

Among the 450 patients, 94 (21%) underwent surgery. Indications for surgery were FNAB diagnosis of malignant or suspicious lesions in 40 of 94 cases (43%), supracentimetric or isolated cold nodule in 24 cases (26%), simultaneous presence of a palpable nodule in a multinodular gland in 16 cases (17%), and miscellaneous reasons in 14 cases (15%; 2 hyperthyroidism, 4 cervical adenopathy, and 7 increasing size of nodule and suspicious echographic features). The final histological diagnosis (according to the WHO classification) after surgical removal was considered the gold standard (9). Seven occult histological carcinomas found outside the biopsied nodule were not taken into account and were considered incidental.

Statistical analyses were performed using the SPSS (SPSS, Inc., Chicago, IL) software package. All statistical analyses involving nodule volume were performed on logarithm-transformed volume data. The relationships between the proportion of ACM and various ultrasonographic features, including nodule size, were explored using logistic regression. A logistic model including such ultrasonographic features to predict histological diagnosis was also designed.

Results

Benign, suspicious, or malignant cytological diagnosis and ICM concerned, respectively, 293 (65%), 50 (11%), 22 (5%), and 85 (19%) of the 450 nodules (Table 2). Table 2 indicates that 42 of 293 (14%) patients with benign cytological results were subjected to surgery. The corresponding data for patients with suspicious, malignant, and ICM results were 24 of 50 (48%), 16 of 22 (73%), and 12 of 85 (14%), respectively. Among the 94 operated nodules, 20 (21%) carcinomas were found at final histology, representing 4% of the population biopsied.

Adequacy of US-FNAB material

Among the 450 nodules subjected to FNAB, 365 (81%) yielded ACM, and 85 (19%) yielded ICM for diagnosis. The mean diameter of the 450 nodules as measured by ultrasonography ranged from 0.43–3.67 cm (mean, 1.33 cm; median, 1.22), and the mean diameter of the 94 operated nodules ranged from 0.57–2.6 cm (mean, 1.29 cm; median, 1.23). Table 3 shows the proportion of ACM according to nodule volume. Considering the partition of the series in ten quantiles, this proportion varied from 64–91%. The observed variation did not significantly differ from linearity ($P < 0.92$), and logistic regression indicated that the proportion of ACM significantly increased ($P < 0.0001$) with the nodule volume.

TABLE 2. Cytological and histological diagnoses according to the nodule sizes

Cytology	Total	Operated	Carcinomas
Infracentimetric nodules			
Total	115	24	8
Benign	64	11	1
Suspicious	9	6	2
Malignant	6	5	4
ICM	36	2	1
Centimetric or supracentimetric nodules			
Total	335	70	12
Benign	229	31	0
Suspicious	41	18	5
Malignant	16	11	5
ICM	49	10	2
All nodules			
Total	450	94	20
Benign	293	42	1
Suspicious	50	24	7
Malignant	22	16	9
ICM	85	12	3

Table 4 details the distribution of US parameters in the series. The logistic model indicates that the proportion of ACM did not significantly differ according to the echostructure ($P < 0.78$), the echogenecity ($P < 0.68$), or the presence of calcifications ($P < 0.46$), but was significantly associated with well defined margins ($P < 0.02$).

Accuracy of US and US-FNAB in the diagnosis of malignancy

The 20 carcinomas diagnosed at final histology corresponded to 16 papillary, 3 follicular, and 1 medullary carcinomas. The ultrasonographic mean diameter of the 20 carcinomas ranged from 0.63–2.27 cm (mean, 1.23 cm; median, 1.08), and 12 of them (60%) were centimetric or supracentimetric.

Diagnosis of malignancy was successfully made by US-FNAB in 16 cases, unequivocally made in 9 cases, strongly suggested in 7 cases, and missed in 4 cases, 3 because of ICM

TABLE 3. Distribution of nodule sizes and corresponding proportions of adequate cytological material (% ACM)

Nodule quantiles	Observed nodules (no.)	Vol (cm^3), observed range	Mean diameter (class mean; observed range)	ACM [no. (%)]
Total	450	00.04–23.78	1,33; 0.43–3.67	365 (81.1)
Class 1	45	00.04–00.23	0,69; 0.43–0.80	29 (64.4)
Class 2	45	00.24–00.38	0,87; 0.80–0.97	31 (68.9)
Class 3	45	00.38–00.50	0,98; 0.93–1.07	35 (77.8)
Class 4	45	00.50–00.64	1,07; 1.00–1.23	33 (73.3)
Class 5	45	00.65–00.84	1,17; 1.10–1.27	39 (86.7)
Class 6	45	00.85–01.05	1,26; 1.20–1.40	38 (84.4)
Class 7	45	01.06–01.53	1,40; 1.30–1.50	38 (84.4)
Class 8	45	01.53–02.05	1,56; 1.47–1.63	40 (88.9)
Class 9	45	02.14–03.85	1,81; 1.63–2.07	41 (91.1)
Class 10	45	03.89–23.78	2,50; 2.03–3.67	41 (91.1)

Nodules were sorted according to their measured volume, and the total sample was then partitioned into 10 quantiles (10 classes, each composed of 10% of the total sample) according to the nodule volumes. For each class, the corresponding nodule volumes (observed range), the mean diameters (mean, observed range), and the corresponding adequate cytological material (ACM) data are shown.

TABLE 4. Distribution of ultrasonographic parameters in the series and corresponding data concerning adequate cytological material (ACM), centimetric and supracentimetric nodules (≥1 cm), and histological diagnosis

	No. (% of total)	≥1 cm [no. (%)[a]]	ACM [no. (%)[a]]	Histological diagnosis of 94 operated cases [no. (%[a])]	
				Benign	Malignant
Total	450 (100)	335 (74)	365 (81)	74 (16)	20 (04)
Echostructure					
Solid	204 (45)	139 (68)	160 (78)	29 (14)	17 (08)
Mixed	213 (47)	172 (81)	178 (84)	39 (18)	3 (01)
Cystic	33 (07)	24 (73)	27 (82)	6 (18)	0 (00)
Echogenecity[b]					
Hypo	296 (66)	217 (73)	236 (80)	51 (17)	18 (06)
Iso	77 (17)	57 (74)	61 (79)	10 (13)	1 (01)
Hyper	44 (10)	37 (84)	41 (93)	7 (16)	1 (02)
Solid + hypo[c]	139 (31)	94 (68)	110 (79)	22 (16)	16 (12)
Nodule margins					
Blurred	95 (21)	60 (63)	67 (71)	18 (19)	11 (12)
Well defined	355 (79)	275 (77)	298 (84)	56 (16)	9 (03)
Calcifications					
Presence	108 (24)	70 (65)	81 (75)	20 (19)	10 (09)
Absence	342 (76)	265 (77)	284 (83)	54 (16)	10 (03)

[a] The denominator used to calculate the percentage is the first number of the line.
[b] Cystic nodules (n = 33) were defined as anechoic nodules.
[c] This line corresponds to nodules both solid and hypoechoic.

and 1 misdiagnosed as a benign cytological result (Table 2). The mean diameters of 2 of 3 missed malignant nodules because of ICM, were supracentimetric (1.1 and 1.6 cm). The sensitivity of US-FNAB diagnosis in the operated nodule sample was 94%, and the specificity was 63% (Table 5). As shown in Table 4, none of the 20 malignant nodules was entirely cystic; 17 (85%) were homogeneously solid, and 3 were mixed (with cystic and solid components). Eighteen (90%) carcinomas were hypoechoic, and only 1 was hyperechoic; 16 (80%) were both homogeneously solid and hypoechoic. Calcifications and blurred margins were found, respectively, in 10 and 11 of the 20 malignant nodules; 7 malignant and 11 benign nodules presented both calcifications and blurred margins.

Logistic regression indicated that a solid hypoechoic feature was a useful criterion to predict malignancy ($P < 0.0003$). When the solid hypoechoic feature was considered the criterion of malignancy, the sensitivity and specificity of US findings for malignancy in the operated nodule sample were 80% and 70%, respectively (Table 5). It should be noted that 45 of the 115 infracentimetric nodules were both solid and hypoechoic (Table 6). Among these, 16 were operated and 7 corresponded to carcinomas at final histology. Conversely, only 1 malignant nodule was found at final histology of the 77 cystic or hyperechoic nodules. Considering other US pa-

TABLE 5. Accuracy of US-FNAB and ultrasonography diagnoses

Index	US-FNAB (n = 82)[a]	Ultrasonography (n = 94)
TN [no. (%)]	41 (50)	52 (55)
TP [no. (%)]	16 (20)	16 (17)
FN [no. (%)]	1 (1)	4 (4)
FP [no. (%)]	24 (29)	22 (23)
% Sensitivity (=TP/[TP + FN])	94	80
% Specificity (=TN/[TN + FP])	63	70
% Positive predictive value (=TP/[TP + FP])	40	42
% Negative predictive value (=TN/[TN + FN])	98	93

TN, true negative; TP, true positive; FN, false negative; FP, false positive.
[a] Nodules with insufficient cytological material (n = 12) were excluded, and suspicious cytological results were handled as malignant diagnoses.

rameters, neither nodule size ($P < 0.6$), the presence of calcification ($P < 0.48$), nor blurred margins ($P < 0.25$) were significantly associated with the histological diagnosis. Benign and malignant nodules had comparable size distributions.

Discussion

FNAB is considered to be the most effective and reliable procedure for the diagnosis of malignant thyroid nodules (2). In the literature, a variability in reported ACM proportions is observed. Several explanations have been proposed: needle size (6, 10), experience in performing FNAB (11, 12), or differences in the populations biopsied (1, 11). Yokozawa *et al.* and Rosen *et al.* report 88% and 68% ACM with US guidance, respectively (13, 14). The proportion of ACM observed in our study (81%) is within the same range. To our knowledge, the role of nodule size has not been investigated. Our results indicate that the proportion of ACM increases with the size of the nodules (Table 3). In our series, the proportion of ACM was 85% in centimetric and supracentimetric nodules and 69% in infracentimetric nodules. US-FNAB allowed the discovery of 10 (50%) supracentimetric of 20 histological carcinomas (Table 2). Therefore, our results indicate that supracentimetric nonpalpable nodules benefit from US-FNAB. Large malignant nodules have been reported to be missed by palpation (15). In a series of 145 nodules, Witterick *et al.* studied the size of 20 malignant nodules confirmed at histology that escaped detection by palpation. The greatest size of malignant nodules was 2.1 cm (15). Rosen *et al.* report 11 of 15 nonpalpable carcinomas with a diameter greater than 1 cm (14). In our study, 12 nonpalpable malignant nodules were centimetric or supracentimetric (Table 2). The existence of these nodules, detected by US exploration, suggests that a simple follow-up neck palpation, as previously proposed (5, 16), may not be the safest management strategy.

Our results indicate that besides size, other ultrasonographic parameters should be considered. In particular, the proportion of ACM was significantly greater for nodules with well defined margins than for nodules with blurred margins (Table 4). The echostructure, the presence of calcifications, and the echogenecity features were not significantly associated with ACM. The useful contribution of US guidance that directs the needle toward the solid component in cystic nodules and avoids a puncture across dense calcifications may explain our results (7, 13). Thus, we conclude that in this series, centimetric and supracentimetric size and well defined margins constitute propitious conditions for the success of the US-FNAB procedure in nonpalpable nodules.

Considering the high prevalence of US thyroid nodules (4), we believe that a systematic US-FNAB would lead to an unjustified burden for health care. Indeed, there is a low chance of detecting cancers (4% of the biopsied population in the present series), and the prognosis of the papillary thyroid microcarcinoma is good (17). The evaluation of strategies for an optimal management of thyroid nonpalpable nodules is still a matter of debate, and our study, as well as others, has some limitations.

First, the techniques are only evaluated on operated patients. Such a sample does not reflect the total biopsied population. Moreover, in most of the series, only a proportion of the malignant and suspicious cytological results are compared to histological results, whereas some patients with benign cytology are subjected to surgery. In our series, the surgical and histological data of 6 patients with malignant cytological results were unknown despite repeated efforts for obtaining information. Conversely, 42 patients with benign cytological results and 12 patients with ICM had surgery for indications detailed in *Subjects and Methods*, and 4 of these 54 patients had carcinoma at final histology (Table 2). The indications for surgery in these 4 cases were as follows: hyperthyroidism, goiter, suspicious US-FNAB results of nonpalpable adenopathy detected by ultrasound, and suspicious cytological results on an associated palpable nodule.

Second, discrepancies in the reported FNAB performances depend on the various ways the suspicious cases are handled in the calculations (18). Some authors only take into consideration benign and malignant cytological results. Others consider suspicious and/or follicular initial diagnosis as a diagnosis of malignancy and classify such cases as true positive even if they correspond to benign microfollicular adenomas (1, 2). In our study, true positive results corresponded to FNAB malignant or suspicious nodules confirmed as carcinomas at final histology.

Third, the value of US-FNAB in nonpalpable nodules has to be balanced with the clinical context. Associated thyroid disease or symptoms were useful and led to an appropriate assessment by US followed by US-FNAB in 12 carcinomas whereas 8 carcinomas were found incidentally, by screening or for questionable indications of US exploration (Table 1).

Nevertheless, our results led us to study the impact of four US-FNAB based strategies in the management of nonpalpable thyroid nodules. The four strategies are shown in Table 6 and are derived from surgical exploration of suspicious and malignant cytological results:

The first strategy, US-FNAB performed on all nodules, will be used as a reference (Table 6). US-FNAB allowed the detection of 16 histological carcinomas and corresponded to a sensitivity of 94%. In other series reported in the literature, the sensitivity and specificity of US-FNAB amounted to 79%

TABLE 6. Detection of histological carcinomas based on suspicious and malignant cytological results according to four strategies of FNAB indication

Sample subjected to FNAB	Total cytologies	Suspicious and malignant cytologies (operated/total)	Detected carcinomas
All nodules	450	40/72	16
Centimetric or supracentimetric nodules	335	29/57	10
Solid hypoechoic nodules	139	21/30	13
Centimetric or supracentimetric or solid hypoechoic nodules	380	36/66	15

and 85%, respectively (6). When reviewing the results of 18,183 FNAB in 7 large series, Gharib and Goellner indicate a sensitivity of the method varying from 65–98% and a specificity varying from 72–100%; the overall accuracy was 95% (1). However, the studies only concern direct FNAB on palpable nodules. Some authors did not detect any significant difference between direct and US-guided FNAB (7). Others indicate that US guidance provides a more precise and adequate sampling with a lower rate of false negatives (19, 20). However, the palpable and nonpalpable nodules are hardly comparable in these studies. Due to the high prevalence of US thyroid nodules, a systematic US-FNAB performed on all nonpalpable nodules is not advisable.

The second strategy refers to a systematic US-FNAB performed only on centimetric and supracentimetric nodules. According to this strategy, only 10 carcinomas would have been detected; 8 of the 10 missed carcinomas would have been infracentimetric. Therefore, such a strategy does not appear advisable.

The third strategy would suggest a US-FNAB on solid and hypoechoic nodules. However, the relevance of US features for predicting malignancy is still not clearly defined. Although the low specificity of US screening of thyroid nodules has been underlined by some authors (21–23), it is generally accepted that solid hypoechoic nodules are suspicious US features (24). In our series, only 31% of the patients would be subjected to FNAB; 13 carcinomas would have been detected, 7 of these being infracentimetric. Conversely, the indication of US-FNAB in cystic or hyperechoic nonpalpable nodules is questionable.

The fourth strategy is to perform US-FNAB on centimetric, supracentimetric, or solid hypoechoic nodules. The interest of such a strategy must be balanced with those of the previous one. With the fourth strategy, 84% of the patients would be subjected to FNAB, but 15 carcinomas would be detected. In our view, this strategy, allowing the detection of carcinomas with the best reliability while avoiding a systematic US-FNAB on all nodules, should be recommended.

In conclusion, US-FNAB must be favorably considered for nonpalpable thyroid nodules, especially for the exploration of centimetric, supracentimetric, or solid hypoechoic nodules. The relative failure of US-FNAB on infracentimetric nodules is outlined and must be balanced with the high proportion of cancers detected in solid and hypoechoic nodules.

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